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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,099	07/14/2003	Rebekka M. Wachter	026069-151480US	8511

20350 7590 06/19/2008

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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
06/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,099	WACHTER ET AL.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *143-146,148-151 and 188-190* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *143-146,148-151 and 188-190* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080409*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9 April 2008 has been entered.

Sequence Disclosure

Applicant's revised Sequence Listing correcting the errors indicated in the Validation Report set forth at in the eleven pages following page 4 of the communication mailed 22 October 2007 is acknowledged. There is no statement, however, among the amendments to the specification filed 9 April 2008 that directs its entry in the specification to replace the earlier version(s) of the Sequence Listing. In response to this communication, Applicant must provide a statement, in the form of an amendment to the specification, directing entry of the Sequence Listing submitted 9 April 2008 in the specification to replace the earlier version(s) of the Sequence Listing.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed 9 April 2008, citing publications provided as Exhibits accompanying the Response, is hereby acknowledged.

Response to Amendment

Applicant's arguments, the Declaration of Dr. Hanson under 37 CFR 1.132, and the exhibits submitted in the Response filed 5 April 2008 are persuasive in establishing that the teachings of the specification, combined with those in the prior art, permit the modification of both the amino acid sequence region of the chromophore itself, interior regions above and below the plane of the chromophore region, and the cylindrical, β-barrel, scaffolding of a *Aequorea* green fluorescent protein [GFP], by concurrent amino acid substitutions. Such modifications include both those made by a person, whether or not disclosed in the specification and naturally-arising amino acid sequence alterations such as the Q80R substitution indicated at page 5 of the Declaration of Dr. Hanson. The specification and the prior art show that it is within the level of skill in the art to concomitantly alter several characteristics of the GFP amino acid sequence set forth in SEQ ID NO:2, including its surface charge, redox status, capacity to aggregate in multimers, and the wavelength of its emission, while nonetheless conserving its structural integrity and capacity to produce light emissions, by combining substitutions disclosed in the

specification and in the prior art with limited, terminal amino acid sequence deletions of the prior art to reach concurrent alteration of as much as 15% of the amino acid positions, 36 positions, in the amino acid sequence of SEQ ID NO:2. However, the amendments of claims 143 and 144 in the Response filed 5 April 2008 deleting recitations of amino acid substitutions at positions 66 and 69 and Applicant's arguments traversing the obviousness type double-patenting rejections of record are not persuasive. The rejections of record are restated below, together with a new rejection on the grounds of obviousness type double-patenting. Terminal Disclaimers over terms of commonly-assigned US Patents Nos. 6,150,176, 6,780,975, and 7,015,310 are required to permit the allowance of claims 143-146, 148-151 and 188-190 pending herein.

Claim Objections

Claims 143, 144, and 150 are objected to because of the following informalities:

1) Claims 143 and 144 place the first recitation of SEQ ID NO:2 in their preambles within parentheses. The sequence identifier, SEQ ID NO:2 is an integral subject matter of both claims and may not be set off from the claims' recitations. To overcome this aspect of the objection, both claims may be amended to remove the parenthetical statements and inserting, "set forth in SEQ ID NO:86".

2) Clauses (i) of claims 143 and 144 fail to properly state the various substitutions at position 148 in the alternative, e.g., by reciting "either" between the pair of substitutions in this clause in claim 143, and by reciting the alternatives in this clause in claim 144 according to the format, " and one of . . . or". Amending clauses (i) of both claims to properly state the alternative subject matters in the alternative will overcome this aspect of the objection.

3) Clauses (ii) of claims 143 and 144 improperly state their intended Markush groups; the proper format requires the use of the conjunction "and" before the final member of the groups, the position 201 sets of substitutions, in both claims. Amending clauses (ii) of both claims to insert the conjunction "and" before "L201S," will overcome this aspect of the objection.

4) Claim 150 improperly recites, "[t]he . . . protein of claim 143, wherein said . . . protein comprises a substitution at position V163", because claim 143 recites no "position V163". Claim 150 must be amended to state "[t]he . . . protein of claim 143, wherein said . . . protein **further** comprises a substitution at position V163", to overcome this aspect of the objection.

Appropriate correction of each of these deficiencies in the claims is required in the response to this communication.

Double Patenting: Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 143-146, 148-151, and 188-190 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 29-37 of U.S. Patent No. 6,150,176 for the reasons set forth in the prior Office action, mailed May 25, 2005. The subject matter of the patented claims falls within the scope of the claims herein as amended 5 April 2008, and the presence or absence of a recitation of a particular position for modification in a pending claim does not alter the scope of the claims based on the disclosure of the specification.

Claims 143-146, 148-151, and 188-190 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of U.S. Patent No. 6,780,975 for the reasons set forth in the prior Office action, mailed May 25, 2005. The subject matter of the patented claims falls within the scope of the claims herein as amended 5 April 2008, and the presence or absence of a recitation of a particular position for modification in a pending claim does not alter the scope of the claims based on the disclosure of the specification.

Claims 143-146, 148-151, and 188-190 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 17-26 of U.S. Patent No. 7,015,310, made of record herewith. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the patented claims falls within the scope of the generic claims 143-146, 148-151, and 188-190 claims herein as amended 5 April 2008 herein, and the presence or absence of a recitation of a particular position for modification in a pending claim does not alter the claims' scope based on the disclosure of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 143-146, 148-151 and 188-190 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a modified fluorescent protein sharing 85% sequence identity with the amino acid sequence of SEQ ID NO:2 that is capable of emitting light within the spectrum of 395-516 nm, does not reasonably provide enablement for the preparation of a modified fluorescent protein sharing 85% sequence identity with the amino acid sequence of SEQ ID NO:2 that is capable of emitting light of wavelengths longer or shorter than this spectrum. Neither does the specification enable the use of a modified fluorescent protein sharing 85% sequence identity with the amino acid sequence of SEQ ID NO:2 that is incapable of emitting light. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention of claims 134, 145, 146, 149-151, 189, and 190, or, in the case of claims 144 and 188, to use a non-fluorescent invention, commensurate in scope with these claims.

It is agreed that the prior art, e.g., Tsien, 1998, and Palm et al., 1997, shows that skilled artisans have made amino acid modifications and have modified buffer conditions, e.g., pH, to alter the emission spectrum of the green fluorescent protein [GFP] amino acid sequence set forth in SEQ ID NO:2 within the spectrum of 395 nm to 516 nm, essentially from red to blue, and that skilled artisans have also quenched fluorescence of the GFP chromophore. Claim 143, however, in the recitation of "said functional engineered fluorescent protein has a different fluorescent property…as compared to…SEQ ID NO:2" encompasses a scope that reaches any conceivable alteration of fluorescent emission, including to, e.g., emission in the infrared, violet, and ultraviolet. Claim 144 describes a modified polypeptide that need not produce any emission, but the specification does not teach any use of such a quenched polypeptide having only an alteration of anion binding affinity. Even though the state of the art shows that the teaching of the specification, combined with the teachings of the prior art will permit concurrent alteration of as much as 15% of the amino acid positions in the amino acid sequence of SEQ ID NO:2 while maintaining both the structural integrity and visible range of fluorescent emission of the GFP, both the specification and the prior art are silent concerning extension of the emission spectrum beyond the visible range.

Instead, the specification and the prior art teach that range of amino acids that might be substituted for the tyrosine and asparagine at the core of the GFP chromophore that will permit fluorescence is quite limited, and that even the range of substituents for the adjacent, amino-proximal serine or threonine, found in the GFP and similar chromophores is limited. Neither the

specification nor the prior art suggest where the amino acid sequence set forth in SEQ ID NO:2 might be modified apart from the GFP chromophore to extend the GFP emission spectrum to wavelengths shorter than red or to longer wavelengths such as violet or the ultraviolet. In addition, the instant specification provides no teaching of the use of a GFP modified to quench fluorescence.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claims and the scope of guidance provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970). The Federal Circuit has approved this standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for extending the emission spectrum of a modified amino acid sequence of SEQ ID NO:2 to an unlimited extent as permitted by claims 134, 145, 146, 149-151, 189, and 190.

b) the specification lacks working examples acid sequence of SEQ ID NO:2 is modified to extend its emission spectrum to an unlimited extent as permitted by claims 134, 145, 146, 149-151, 189, and 190,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration and instead teach away from it,

d) unpredictability exists in the art where no members of the class of fluorescent proteins having a serine/threonine - tyrosine - glycine chromophore core have been altered to produce fluorescent emissions in the infrared, violet, or ultraviolet as permitted by claims 134, 145, 146, 149-151, 189, and 190, and

e) the specification lacks adequate, specific, guidance for using an entirely quenched, non-fluorescent protein resulting from a modification of SEQ ID NO:2 that alters its anion binding affinity according to claim 144 and 188.

Thus the broad scope of modification of SEQ ID NO:2 embraced by the phrase, "a different fluorescent property", is unsupported by the present specification even if taken in combination with teachings available in the prior art and the specification fails to teach the use of a modified SEQ ID NO:2 having no fluorescence but a different anion binding affinity.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/David J. Steadman/
David Steadman, Ph.D.
Primary Examiner
Art Unit 1656

/William W. Moore/
William W. Moore
3 June 2008